Journal of Translational Autoimmunity 4 (2021) 100118

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

Diagnosis and treatment of eosinophilic myocarditis

Zezhong Zhong [a,*], Zicong Yang [b], Yiming Peng [a], Lei Wang [a], Xuming Yuan [a]

[a] Department of Cardiology, Liuyang People's Hospital, Nanhua University, Hunan Province, 410300, China
[b] People's Hospital of Guangxi Zhuang Autonomous Region, 530021, China

ARTICLE INFO

Keywords:
Eosinophilic myocarditis
Cardiac magnetic resonance
Endomyocardial biopsy
Glucocorticoids

ABSTRACT

Eosinophilic myocarditis is a type of inflammatory cardiomyopathy characterized by eosinophilic infiltration into myocardial tissue. The accurate myocarditis incidence rate is difficult to determine because of the clinical limitations of an endomyocardial biopsy. The primary pathogenesis of eosinophilic myocarditis is the release of related substances by eosinophils, leading to cell membrane damage and cell destruction. However, evidence suggests that specific genes play a role in myocarditis development.As CMR imaging availability increases, the diagnosis rate of eosinophilic myocarditis will increase. The diagnosis of myocarditis mainly depends on an endocardial biopsy. Glucocorticoids can relieve patients' symptoms, but the early use of steroids may prevent intermediate disease stage development (i.e., thrombonecrosis and fibrosis with wall thrombosis). Anticoagulant therapy may also affect disease development. In addition to routine follow-up, a regular myocardial biopsy should be considered for discharged patients, if possible.

1. Introduction

Eosinophilic myocarditis is a type of inflammatory cardiomyopathy characterized by eosinophilic infiltration into myocardial tissue. A correlation between eosinophils and heart disease is uncommon. The first discovery was endocarditis, reported by Löfflter in 1935 [1] and pathologically characterized by eosinophilic infiltration of endocardial cells and the formation of myocardial fibrosis.

2. Prevalence of eosinophilic myocarditis

Determining the accurate myocarditis incidence rate is difficult because of the clinical limitations of an endomyocardial biopsy. Some studies on sudden cardiac death in young individuals, upon autopsy, found that 2%–42% of the dead suffered from myocarditis [2,3]. Similarly, 9%–16% of unexplained adult patients with non-ischemic dilated cardiomyopathy [4,5] and 46% of pediatric patients with dilated cardiomyopathy [6] were diagnosed with myocarditis by biopsy. Generally, if the patient's symptoms are not serious and heart dysfunction is not obvious, most myocarditis cases are self-healing. However, about 30% of patients with biopsy-confirmed myocarditis progress to dilated cardiomyopathy, resulting in a poor prognosis. Myocarditis manifestations are also found upon autopsies of patients with non-cardiac death or in myocardial specimens wherein myocarditis was not suspected, such as heart transplantation patients who underwent heart valve-related surgery or used myocardial contractile drugs [7]. Most of these patients lack the clinical manifestations of cardiomyopathy, but may have related pathological changes. However, it is difficult to diagnose the clinical significance of myocarditis.

3. Eosinophilic myocarditis etiology

The etiology of myocarditis is roughly divided into three parts: infection, autoimmunity, and heart poison. Viral infections are the most prominent cause of myocarditis, especially the Coxsackie-B virus. Specifically, sumatriptan [8] and canine Toxoplasma infections [9] have been linked to eosinophilic myocarditis. Eosinophilia, or the increase in eosinophil count, has a similar etiology to eosinophilic myocarditis. The causes include myelodysplasia, allergies, parasites, viral infections, and tumors.

Abbreviations: ECP, eosinophilic cationic protein; ANCA, anti-neutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; IFNγ, interferon gamma; EAM, experimental autoimmune myocarditis; FIP1L1-PDGFRA, FIP1-like1-platelet-derived growth factor receptor α; ECG, electrocardiogram; CMR, cardiac magnetic resonance; EGE, early gadolinium enhancement, LGE, late gadolinium enhancement; EMB, endomyocardial biopsy; CEL, chronic eosinophilic leukemia..

* Corresponding author.
E-mail address: zhongzezhong@163.com (Z. Zhong).

https://doi.org/10.1016/j.jtauto.2021.100118
Received 30 May 2021; Received in revised form 25 August 2021; Accepted 30 August 2021
Available online 2 September 2021

4. Eosinophilic myocarditis pathophysiology

Myocarditis is histologically diagnosed as lymphocytic, pleomorphic, giant cell, eosinophilic, or cardiac sarcoidosis based on the types of inflammatory cell infiltration. Eosinophilic myocarditis is not often diagnosed. The primary pathological changes in myocarditis include myocardial edema, capillary leakage, hyperemia, cell necrosis, and fibrosis scar formation.

4.1. Possible myocardial injury mechanisms

Most patients with eosinophilic myocarditis had cardiac insufficiency and myocardial injury. There are four possible mechanisms: direct damage of eosinophils, related substance release, endogenous coagulation activation, and autoimmune system activation.

4.1.1. Direct damage of eosinophils

Direct damage of eosinophils may cause eosinophilic myocarditis. Studies have shown that the number of degraded eosinophils in the heart tissue may be more important than the total number of eosinophils [10]. However, another report indicated that the severity of heart damage does not necessarily correspond to the degree of blood eosinophilia [11].

4.1.2. Related substance release

Another possible mechanism involves the release of related substances from eosinophils, leading to cell membrane damage. Previous studies showed that cardiomyocyte necrosis was related to eosinophil degranulation and eosinophil major basic protein deposition. Therefore, the mechanism may be related to increased membrane permeability and mitochondrial respiratory inhibition caused by eosinophil major basic protein [12,13]. Eosinophils express granulocyte/macrophage colony-stimulating factor, interleukin (IL)-3, and IL-5 receptors [14]. IL-5 is an eosinophilic leukopoietin that activates the proliferation and differentiation of eosinophil precursors and stimulates mature eosinophils at inflammatory sites [15]. IL-5 produced by eosinophils may play a major role in the chemical attraction and degranulation of eosinophils [16], such as eosinophilic cationic protein (ECP). Kishimoto et al. [17] demonstrated the cardiotoxicity of ECP in animal preparations, and in vitro studies demonstrated that ECP induced histamine and tryptase release from human cardiac mast cells [18]. Pretreating eosinophils with corticosteroids reduced ECP release [19].

An immunohistochemical study of myocardial biopsies demonstrated that the monoclonal antibody EG2 was specific for activating eosinophils, binding ECP, and eosinophil protein X secretory type [20]. However, many cases reported that endomyocardial biopsy showed eosinophil degranulation, extracellular deposition of eosinophil major basic protein, and ECP near thrombotic and necrotic lesions [12,21,22].

4.1.3. Endogenous coagulation activation

Eosinophils activate the endogenous coagulation mechanism, leading to vascular endothelium destruction and microcirculation thrombosis formation, causing myocardial ischemia and myocardial necrosis. Some cases also reported myocardial thrombosis and endocardial small vessel thrombosis [21], while others found mural thrombus in some patients [23].

4.1.4. Autoimmune system activation

Eosinophils activate the autoimmune system similar to autoimmune injury. Persistent infection and inflammation may be responsible for releasing autoantigens from the heart that were previously hidden from the immune system. A report also suggested that pre-existing immune changes (e.g., viral antigen stimulation or autoimmune diseases) change the myocardial microenvironment and facilitate eosinophil localization and degranulation [24].

4.1.5. Mechanisms summary

Presently, studies have confirmed three of the four potential mechanisms (sections 4.1.1, 4.1.2, and 4.1.3). The fourth mechanism (section 4.1.4) currently has no direct evidence, but this theory should be explored in future research. Gottdiener et al. described eosinophil damage to heart tissue in three stages: acute necrosis stage, thrombosis stage, and fibrous scarring, but now there is evidence suggesting that early interstitial fibrosis also exists. Combined with pathophysiological characteristics, scar tissue and fibrosis can form after cell necrosis and apoptosis. Necrosis, thrombosis, and fibrous scarring are likely to coexist. Therefore, some hypothesize that eosinophilic myocarditis, Löfflter endocarditis, Davis disease, and myocardial intimal fibrosis are different stages of a single disease caused by eosinophil-mediated heart injury [25].

5. Eosinophilic myocarditis versus related diseases

Cardiomyopathy is primarily classified by morphology. Dilated cardiomyopathy is a clinical diagnosis based on the morphological and functional characteristics of the left ventricle, whereas inflammatory cardiomyopathy is a histological and functional diagnosis characterized by myocarditis with cardiac systolic or diastolic dysfunction. Therefore, dilated cardiomyopathy and myocarditis are not independent of each other.

Generally, there are few eosinophil-related diseases. Regarding cardiovascular diseases, Lofflter endocarditis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are similar. ANCA-associated vasculitis is a group of systemic small vasculitis characterized by the presence of ANCA in serum. Pathologically, it is characterized by full-thickness inflammation and necrosis and can be with or without small vessel granuloma formation. Further, there is cellulose-like necrosis and infiltration of neutrophils, lymphocytes, eosinophils, and other cells. ANCA-associated vasculitis mainly involves small vessels, but can also involve small and medium-sized arteries and is rarely positive in large and medium vasculitis. ANCA-associated vasculitis includes microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis.

EGPA is formerly known as allergic granulomatosis vasculitis or Churg-Strauss syndrome and primarily manifests as vascular wall inflammation, necrosis, and destruction. A pathological biopsy is a gold standard for diagnosis, and current case reports indicate that the most notable pathological features are inflammatory cell infiltration, cellulose-like necrosis, granuloma formation, stenosis, occlusion, and thrombosis.

Hypereosinophilic syndrome (HES), also known as idiopathic hypereosinophilic syndrome, is a rare clonal proliferative hematopathy of bone marrow progenitor cells. Heart disease is the main cause of HES morbidity and mortality, with an incidence rate between 48% and 75% [26,27]. Eosinophilic myocarditis associated with hypereosinophilic syndrome is usually less painful than acute necrotizing eosinophilic myocarditis and lasts for weeks or months [28].

Additionally, previously eosinophilic myocarditis has the rest of the name, such as hypersensitivity (or allergic) myocarditis. Allergic myocarditis is characterized by rash, fever, sinus tachycardia, and drug-related eosinophilia, as well as myocardial eosinophil and lymphocyte infiltration, but necrosis is uncommon [29]. A theory by Parrillo et al. suggests that acute necrotizing eosinophilic myocarditis may be severe hypersensitive myocarditis [30]. However, from a pathological point of view, hypersensitive myocarditis may be a manifestation of eosinophilic myocarditis. Necrotizing eosinophilic myocarditis differs from typical hypersensitive myocarditis in that the lesion is diffuse rather than perivascular and interstitial, and myocardial cell necrosis is prominent.

6. Advances in the genetics of eosinophilic myocarditis

Regarding genetics, evidence suggests that specific genes play a role

in the occurrence and development of myocarditis. Barin et al. [31] demonstrated that mice lacking both interferon gamma (IFNγ) and IL-17A have severe and rapidly fatal experimental autoimmune myocarditis (EAM), characterized by extensive eosinophil infiltration, myocardial cell necrosis, and thrombosis. The cytokines synergistically inhibit their invasive T-helper-2 cell differentiation and eosinophilic heart infiltration. Eosinophil gene ablation can reverse the IFNγ, IL-17A, and EAM mortality. Further, FIP1-like1-platelet-derived growth factor receptor α (FIP1L1-PDGFRA) was positive in some chronic eosinophilic leukemia patients.

7. Clinical manifestations and laboratory markers

The clinical manifestations of eosinophilic myocarditis patients are generally nonspecific, such as acute chest pain, chest tightness, shortness of breath, and elevated creatine kinase-MB and troponin levels. Severe cases may have a cardiogenic shock. Some cases had allergic diseases before onsets, such as bronchial asthma, rhinitis, or urticaria, while some had common cold symptoms, such as fever, sore throat, and cough. Some cases also met the myocardial infarction diagnostic criteria. In the absence of other evidence, patients are easily misdiagnosed.

ECP may be a useful marker as specificity was higher than in other tests, and the ECP serum concentration increased significantly in some patients [8]. The ECP level was also associated with eosinophilic myocarditis activity. After reducing corticosteroid treatment, the serum ECP level increased again [32]. Therefore, changes in the serum ECP concentration could help determine if the treatment was effective.

8. Electrocardiogram (ECG)

ECG is a routine noninvasive examination, and ECG myocarditis manifestations include ST-T changes, atrioventricular block, bundle branch block, and ventricular arrhythmia (Table 2). Therefore, ECG has no specific performance in the diagnosis of myocarditis.

9. Echocardiography

Color Doppler ultrasound is another routine noninvasive examination that can provide patients with information regarding the heart valve, heart structure, ventricular wall motion, and the presence of ventricular wall edema, mural thrombus, and pericardial effusion [33]. However, many factors affect the accuracy of cardiac color Doppler ultrasound results, and patients with definite diseases may receive false-negative results. However, multiple color Doppler ultrasounds could help to eliminate certain interference factors.

10. Coronary angiography

Coronary angiography cannot diagnose myocarditis, but patients with myocarditis sometimes show acute coronary syndromes, such as chest pain, troponin elevation, and ST-T changes. Therefore, coronary angiography is helpful to exclude acute coronary disease.

11. Cardiac magnetic resonance (CMR) imaging

Eosinophilic myocarditis is a rare disease. The incidence rate is low, but there is a possibility of misdiagnosis and missed diagnoses. Recent economic and technological developments allow CMR examinations to be performed in regional and sub-level medical institutions. As CMR imaging availability increases, the diagnosis rate of eosinophilic myocarditis will increase.

Several eosinophilic myocarditis indicators can be observed via CMR imaging. For example, myocardial edemas are detectable from local or diffuse hyperintensity on T2-weighted imaging. However, turbo inversion recovery magnitude imaging is more sensitive. Further, capillary leakage and congestion can be detected by EGE. Local EGE indicates focal inflammation. However, diffuse EGE requires a calculation of the early gadolinium enhancement rate. LGE can identify myocardial necrosis and fibrous scars by subepicardial enhancement of the left ventricular lateral wall, which is a characteristic manifestation of myocarditis, followed by the ventricular septum. Finally, 32%–57% of myocarditis patients have pericardial effusion. CMR imaging can accurately evaluate the amount, distribution, and hemodynamic significance of pericardial effusion.

CMR imaging has high specificity in diagnosing myocarditis, particularly when the sensitivity and specificity meet the Lewis Lake diagnostic criteria (Table 1) [34]. A case report presented by Chun et al. [35] used CMR imaging when myocarditis emerged and at the follow-up three weeks later and found that the entire left ventricle had diffuse subendocardial LGE. After steroid treatment, CMR imaging showed that the subendocardial LGE decreased significantly, showing acute inflammation and necrosis. However, from an imaging characteristic perspective, CMR imaging can accurately identify myocardial edema, but it cannot accurately determine the cause of the disease. The diagnosis still requires pathological evidence.

12. Endomyocardial biopsy (EMB) and pathological examination

An endocardial biopsy is the gold standard for myocarditis diagnosis and plays an important role in disease development after discharge. One study reported that EMB showed that the eosinophilic myocardial infiltration almost completely subsided, and there was significant clinical recovery after two weeks of treatment [36]. Further, endomyocardial biopsy specimens obtained 60 days after the first biopsy showed that eosinophilic myocarditis subsided, accompanied by alternative fibrosis and normal myocardium [24]. However, myocardial biopsy has several issues, such as requiring technical support and causing trauma. The biopsy is also not very sensitive (approximately 50%) because the infiltration is usually focal [37]. Acute myocardial infarction, left ventricular mural thrombosis, or aneurysm formation are myocardial cell biopsy contraindications. The myocardial cell biopsy risks increase with

Table 1
Cardiac magnetic resonance diagnostic criteria for myocarditis.

In the setting of clinically suspected myocarditis, CMR findings are consistent with myocardial inflammation, if at least 2 of the following criteria are present: Regional or global myocardial SI increase in T2-weighted images. † Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images.‡ There is at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (“late gadoliniumenhancement”).§
A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present.
A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if none of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation. One of the criteria is present.
The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis
†Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; global signal intensity (SI) increase has to be quantified by an SI ratio of myocardium over skeletal muscle of ≥2.0). If the edema is more subendocardial or transmural in combination with a colocalized ischemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported. ‡Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; a global SI enhancement ratio of myocardium over skeletal muscle of ≥4.0 or an absolute myocardial enhancement of ≥45% is consistent with myocarditis. §Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is colocalized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.

Table 2
Guidelines for diagnosing eosinophilic myocarditis.

1. Essential matters
   1) Eosinophilia more than 500/μL
   2) Cardiac symptoms such as chest pain, dyspnea and palpitation
   3) Elevated levels of cardiac enzymes such as CK-MB and Troponin T
   4) ECG changes
   5) Transient hypertrophy or wall motion asynergy of left ventricle in ultrasonography
2. Referencing matters
   1) One third of the cases have allergic disease such as bronchial asthma, rhinitis or urticaria
   2) Prior to the onset of eosinophilic myocarditis, two thirds of cases have the symptoms of a common cold, such as fever, sore throat and cough.
3. Endomyocardial biopsy

The infiltration of eosinophils, degranulation of eosinophils, myocytolysis and necrosis of myocytes. Interstitional edema or fibrosis are observed. In some cases, endomyocarditis is observed.

Eosinophilic myocarditis is strongly considered when the following 5 essential matters are fulfilled. Coronary angiography is recommended to exclude acute myocardial infarction. Definite diagnosis is supported by endomyocardial biopsy.

obvious enlargement of the heart, severe cardiac insufficiency, and recent infection and are further magnified when other diseases cannot be ruled out. Therefore, myocardial cell biopsy implementation is limited.

Additionally, if the patient has pericardial effusion, then the pericardial effusion cytology will show a large number of eosinophils. An analysis of cytokine levels showed that the IL-5 and IL-13 concentrations in pericardial effusion were extremely high, and the IL-5 concentration in peripheral blood was relatively high in the early stage of pericardial drainage [38].

13. Diagnosis

Presently, there are only a few published guidelines for eosinophilic myocarditis, mainly from Europe and Japan (Tables 2 and 3) [39]. The Japanese diagnostic guidelines are not specific and may report relevant manifestations in other diseases. Moreover, the guidelines do not mention the role of CMR imaging in diagnosis. Therefore, we recommend the diagnostic criteria proposed by the European consensus.

Table 3
Diagnostic criteria for clinically suspected myocarditis.

Clinical presentations A
- acute chest pain, pericarditic, or pseudo-ischaemic
- New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Subacute/chronic (3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
- Unexplained cardiogenic shock

Diagnostic criteria

I. ECG/Holter/stress test features

Newly abnormal 12 lead ECG and/or Holter and/or stress testing,any of the following: Ito III degree atrioventricular block,or bundle branch block,ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia

II. Myocardiocytolysis markers

Elevated TnT/TnI

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)

New,otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects):regional Wall motion or global systolicordiastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi

IV. Tissue characterization by CMR

Edema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis if ≥ 1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g., valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria. a If the patient is asymptomatic ≥2 diagnostic criteria should be met.

14. Treatment

Currently, there is no large-scale clinical trial for an eosinophilic myocarditis drug therapy. The treatments that exist primarily include symptomatic and immunosuppressive therapies. However, if there is a confirmed parasite infection, albendazole can be considered.

The main purpose of symptomatic treatment is to maintain life and prevent sudden death, as most patients showed impaired cardiac function. Together with conventional anti-heart failure treatments, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and aldosterone receptor antagonists can improve myocardial remodeling. Further, as most patients have an arrhythmia, careful attention should be given to preventing malignant arrhythmia, which can induce sudden cardiac death. In the case of ineffective conventional drug treatment, mechanical adjuvant therapy, such as a ventricular assist device [40], intra-aortic balloon counterpulsation [41], and extracorporeal membrane oxygenation [42], can be considered to help patients through the riskiest heart failure period. Reports also suggested that patients with pericardial effusion as the main manifestation recovered rapidly after pericardial drainage without corticosteroid treatment [38].

In most cases, glucocorticoids effectively relieved the patients' symptoms, which may be related to the strong anti-inflammatory effect of glucocorticoids. Using steroids early may prevent further development to the intermediate thrombotic necrosis and fibrosis stage with mural thrombosis [43]. Meanwhile, some case reports suggested that cyclophosphamide or methotrexate alone achieved good results without glucocorticoid treatment. Steroids combined with azathioprine [44] also achieved good results.

The effectiveness of anti-inflammatory and immunosuppressive therapy also indicates that eosinophilic myocarditis could be an autoimmune disease. However, further research is needed because there is no obvious, highly sensitive, and specific autoimmune antibody. Regarding drug therapies, rituximab, a monoclonal antibody against $CD20^{+}$ B cells, could be tried.

The IL-5 monoclonal antibody may also have a curative effect. In a previous animal experiment [45], interleukin-5 (IL-5) stimulated eosinophil function and prolonged survival time in vitro. It has been previously reported [46] that in the case of ineffective treatment with high-dose prednisone and immunosuppressants, treatment with anti-interleukin-5, namely mepolizumab, is effective, which can significantly improve cardiac function and reduce pericardial effusion. Moreover, mabolizumab can also be used as a supplement to steroid therapy in EM. When combined with mebolizumab, the steroid dose can be reduced, which may prevent or reduce the side effects caused by steroids. In addition, some animal experiments [47] confirmed that immunostimulatory DNA sequence can inhibit IL-5 in mice. Both ISS and corticosteroids inhibit the production of IL-5, and IL-5 can induce the release of eosinophils in bone marrow. Therefore, ISS inhibits the production of IL-5 and prevents the bone marrow release of eosinophils.

The application of immunoglobulin has been proved to be effective in some patients with eosinophilic myocarditis [48]. However, further research and evidence are needed. Moreover, in a controlled trial [49], IVIG did not enhance LVEF improvement in adults with less than 6-month history of dilated cardiomyopathy. The effect of immunoglobulin on myocarditis continues to remain controversial.

FIP1L1-PDGFRA was positive in CEL patients and imatinib treatment [50]. Other drugs for treating systemic eosinophilic syndromes, such as hydroxyurea, interferon-α, and Imatinib mesylate, are still experimental, and there is no indication that large-scale drug trials are

planned.

Anticoagulant therapy may also affect disease development. Some patients had mural and intravascular thrombus, suggesting that the disease may lead to a hypercoagulable state. The long-term use of hormones can also lead to changes in coagulation function and induce thrombosis. Some patients had no obvious aggravation after anticoagulation treatment [38], indicating that the anticoagulation treatment was harmless, but applying anticoagulants requires further clinical research.

14.1. Prognosis and follow-up

There are no specific data regarding the prognosis of eosinophilic myocarditis. Approximately 10% of patients will die during hospitalization, and approximately 30% of patients will survive less than three years. Regular myocardial biopsy after discharge is meaningful. Therefore, in addition to routine follow-up, regular endomyocardial biopsy should be considered for discharged patients, if possible.

15. Conclusion

Eosinophilic myocarditis is a rare disease, and its etiology and pathogenesis warrant further study. Since the disease is characterized by eosinophils, expanding our understanding of its relationship with other diseases is necessary. The prognosis of patients with eosinophilic myocarditis is poor. Therefore, continuous efforts regarding treatments are needed.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

References

[1] W. Löffler, Endocarditis parietalis fibroplastica mit Bluteosinophilie, Schweiz. Med. Wochenschr. 65 (1936) 817–820.
[2] I. Gore, O. Saphir, Myocarditis; a classification of 1402 cases, Am. Heart J. 34 (1947) 827–830, https://doi.org/10.1016/0002-8703(47)90147-6.
[3] C. Basso, F. Calabrese, D. Corrado, G. Thiene, Postmortem diagnosis in sudden cardiac death victims: Macroscopic, microscopic and molecular findings, Cardiovasc. Res. 50 (2001) 290–300, https://doi.org/10.1016/s0008-6363(01)00261-9.
[4] J.W. Mason, J.B. O'Connell, A. Herskowitz, N.R. Rose, B.M. McManus, M. E. Billingham, T.E. Moon, A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis Treatment Trial Investigators, N. Engl. J. Med. 333 (1995) 269–275, https://doi.org/10.1056/NEJM199508033330501.
[5] G.M. Felker, W. Hu, J.M. Hare, R.H. Hruban, K.L. Baughman, E.K. Kasper, The spectrum of dilated cardiomyopathy. The Johns Hopkins experience with 1,278 patients, Medicine (Baltim.) 78 (1999) 270–283, https://doi.org/10.1097/00005792-199907000-00005.
[6] J.A. Towbin, A.M. Lowe, S.D. Colan, L.A. Sleeper, E.J. Orav, S. Clunie, J. Messere, G.F. Cox, P.R. Lurie, D. Hsu, C. Canter, J.D. Wilkinson, S.E. Lipshultz, Incidence, causes, and outcomes of dilated cardiomyopathy in children, J. Am. Med. Assoc. 296 (2006) 1867–1876, https://doi.org/10.1001/jama.296.15.1867.
[7] J.J. Takkenberg, L.S. Czer, M.C. Fishbein, D.J. Luthringer, A.W. Quartel, J. Mirocha, C.A. Queral, C. Blanche, A. Trento, Eosinophilic myocarditis in patients awaiting heart transplantation, Crit. Care Med. 32 (2004) 714–721, https://doi.org/10.1097/01.ccm.0000114818.58877.06.
[8] M. Arima, T. Kanoh, Eosinophilic myocarditis associated with dense deposits of eosinophil cationic protein (ECP) in endomyocardium with high serum, ECP. Heart. 81 (1999) 669–671, https://doi.org/10.1136/hrt.81.6.669.
[9] K. Enko, T. Tada, K.O. Ohgo, S. Nagase, K. Nakamura, K. Ohta, S. Ichiba, Y. Ujike, Y. Nawa, H. Maruyama, T. Ohe, K.F. Kusano, Fulminant eosinophilic myocarditis associated with visceral larva migrans caused by Toxocara canis infection, Circ. J. 73 (2009) 1344–1348, https://doi.org/10.1253/circj.cj-08-0334.
[10] C.J. Spry, J. Davies, P.C. Tai, E.G. Olsen, C.M. Oakley, J.F. Goodwin, Clinical features of fifteen patients with the hypereosinophilic syndrome, Q. J. Med. 52 (1983) 1–22.
[11] J.E. Parrillo, A.S. Fauci, S.M. Wolff, Therapy of the hypereosinophilic syndrome, Ann. Intern. Med. 89 (1978) 167–172, https://doi.org/10.7326/0003-4819-89-2-167.
[12] P.C. Tai, D.J. Hayes, J.B. Clark, C.J. Spry, Toxic effects of human eosinophil products on isolated rat heart cells in vitro, Biochem. J. 204 (1982) 75–80, https://doi.org/10.1042/bj2040075.
[13] J.D. Young, C.G. Peterson, P. Venge, Z.A. Cohn, Mechanism of membrane damage mediated by human eosinophil cationic protein, Nature 321 (1986) 613–616, https://doi.org/10.1038/321613a0.
[14] K. Toba, T. Koike, A. Shibata, S. Hashimoto, M. Takahashi, M. Masuko, T. Azegami, H. Takahashi, Y. Aizawa, Novel technique for the direct flow cytofluorometric analysis of human basophils in unseparated blood and bone marrow, and the characterization of phenotype and peroxidase of human basophils, Cytometry 35 (1999) 249–259, https://doi.org/10.1002/(SICI)1097-0320(19990301)35:3<249::AID-CYTO8>3.0.CO;2-O.
[15] C. Sillaber, K. Geissler, R. Scherrer, R. Kaltenbrunner, P. Bettelheim, K. Lechner, P. Valent, Type beta transforming growth factors promote interleukin-3 (IL-3)-dependent differentiation of human basophils but inhibit IL-3-dependent differentiation of human eosinophils, Blood 80 (1992) 634–641.
[16] P. Desreumaux, A. Janin, S. Dubucquoi, M.C. Copin, G. Torpier, A. Capron, M. Capron, L. Prin, Synthesis of interleukin-5 by activated eosinophils in patients with eosinophilic heart diseases, Blood 82 (1993) 1553–1560.
[17] C. Kishimoto, C.J. Spry, P.C. Tai, N. Tomioka, C. Kawai, The in vivo cardiotoxic effect of eosinophilic cationic protein in an animal preparation, Jpn. Circ. J. 50 (1986) 1264–1267, https://doi.org/10.1253/jcj.50.1264.
[18] V. Patella, G. de Crescenzo, I. Marinò, A. Genovese, M. Adt, G.J. Gleich, G. Marone, Eosinophil granule proteins activate human heart mast cells, Journal of Immunology 157 (1996) 1219–1225, 1996.
[19] I. Winqvist, T. Olofsson, I. Olsson, Mechanisms for eosinophil degranulation; release of the eosinophil cationic protein, Immunology 51 (1984) 1–8.
[20] P.C. Tai, C.J. Spry, C. Peterson, P. Venge, I. Olsson, Monoclonal antibodies distinguish between storage and secreted forms of eosinophil cationic protein, Nature 309 (1984) 182–184, https://doi.org/10.1038/309182a0.
[21] R. Amini, C. Nielsen, Eosinophilic myocarditis mimicking acute coronary syndrome secondary to idiopathic hypereosinophilic syndrome: a case report, J. Med. Case Rep. 4 (2010) 40, https://doi.org/10.1186/1752-1947-4-40.
[22] D.E. deMello, H. Liapis, S. Jureidini, S. Nouri, G.M. Kephart, G.J. Gleich, Cardiac localization of eosinophil-granule major basic protein in acute necrotizing myocarditis, N. Engl. J. Med. 323 (1990) 1542–1545, https://doi.org/10.1056/NEJM199011293232207.
[23] L. Galiuto, M. Enriquez-Sarano, G.S. Reeder, H.D. Tazelaar, J.T. Li, F.A. Miller, G. J. Gleich, Eosinophilic myocarditis manifesting as myocardial infarction: early diagnosis and successful treatment, Mayo Clin. Proc. 72 (1997) 603–610, https://doi.org/10.4065/72.7.603.
[24] M.A. Getz, R. Subramanian, T. Logemann, F. Ballantyne, Acute necrotizing eosinophilic myocarditis as a manifestation of severe hypersensitivity myocarditis. Antemortem diagnosis and successful treatment, Ann. Intern. Med. 115 (1991) 201–202, https://doi.org/10.7326/0003-4819-115-3-201.
[25] E.G. Olsen, C.J. Spry, Relation between eosinophilia and endomyocardial disease, Prog. Cardiovasc. Dis. 27 (1985) 241–254, https://doi.org/10.1016/0033-0620(85)90008-8.
[26] F. Brito-Babapulle, The eosinophilias, including the idiopathic hypereosinophilic syndrome, Br. J. Haematol. 121 (2003) 203–223, https://doi.org/10.1046/j.1365-2141.2003.04195.x.
[27] S.R. Ommen, J.B. Seward, A.J. Tajik, Clinical and echocardiographic features of hypereosinophilic syndromes, Am. J. Cardiol. 86 (2000) 110–113, https://doi.org/10.1016/s0002-9149(00)00841-9.
[28] P.F. Weller, G.J. Bubley, The idiopathic hypereosinophilic syndrome, Blood 83 (1994) 2759–2779, https://doi.org/10.1182/blood.V83.10.2759.2759.
[29] J.J. Fenoglio Jr., H.A. McAllister Jr., F.G. Mullick, Drug related myocarditis. I. Hypersensitivity myocarditis, Hum. Pathol. 12 (1981) 900–907, https://doi.org/10.1016/s0046-8177(81)80195-5.
[30] J.E. Parrillo, Heart disease and the eosinophil, N. Engl. J. Med. 323 (1990) 1560–1561, https://doi.org/10.1056/NEJM199011293232211.
[31] J.G. Barin, G.C. Baldeviano, M.V. Talor, L. Wu, S. Ong, D. Fairweather, D. Bedja, N. R. Stickel, J.A. Fontes, A.B. Cardamone, D. Zheng, K.L. Gabrielson, N.R. Rose, D. Cihákova, Fatal eosinophilic myocarditis develops in the absence of IFN-gamma and IL-17A, J. Immunol. 191 (2013) 4038–4047, https://doi.org/10.4049/jimmunol.1301282.
[32] M. Arima, T. Kanoh, Y. Kawano, T. Oigawa, S. Yamagami, S. Matsuda, Serum levels of eosinophil cationic protein in patients with eosinophilic myocarditis, Int. J. Cardiol. 84 (2002) 97–99, https://doi.org/10.1016/s0167-5273(02)00074-8.
[33] J.S. Gottdiener, B.J. Maron, R.T. Schooley, J.B. Harley, W.C. Roberts, A.S. Fauci, Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome. Anatomic basis of mitral regurgitation and peripheral embolization, Circulation 67 (1983) 572–578, https://doi.org/10.1161/01.cir.67.3.572.
[34] M.G. Friedrich, U. Sechtem, J. Schulz-Menger, G. Holmvang, P. Alakija, L. T. Cooper, J.A. White, H. Abdel-Aty, M. Gutberlet, S. Prasad, A. Aletras, J.P. Laissy, I. Paterson, N.G. Filipchuk, A. Kumar, M. Pauschinger, P. Liu, International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis, Cardiovascular magnetic resonance in myocarditis: a JACC White Paper, Journal of the American College of Cardiology 53 (2009) 1475–1487, https://doi.org/10.1016/j.jacc.2009.02.007, 2009.
[35] W. Chun, T.M. Grist, T.J. Kamp, T.F. Warner, T.F. Christian, Images in cardiovascular medicine. Infiltrative eosinophilic myocarditis diagnosed and

localized by cardiac magnetic resonance imaging, Circulation 110 (2004) e19, https://doi.org/10.1161/01.CIR.0000135586.94417.3C.
[36] T. Fozing, N. Zouri, A. Tost, R. Breit, G. Seeck, C. Koch, C. Oezbek, Management of a patient with eosinophilic myocarditis and normal peripheral eosinophil count: case report and literature review, Circulation. Heart Failure. 7 (2014) 692–694, https://doi.org/10.1161/CIRCHEARTFAILURE.114.001130.
[37] A.P. Burke, J. Saenger, F. Mullick, R. Virmani, Hypersensitivity myocarditis, Arch. Pathol. Lab Med. 115 (1991) 764–769.
[38] R. Kazama, Y. Okura, M. Hoyano, K. Toba, Y. Ochiai, N. Ishihara, T. Kuroha, T. Yoshida, O. Namura, M. Sogawa, Y. Nakamura, N. Yoshimura, K. Nishikura, K. Kato, H. Hanawa, Y. Tamura, S. Morimoto, M. Kodama, Y. Aizawa, Therapeutic role of pericardiocentesis for acute necrotizing eosinophilic myocarditis with cardiac tamponade, Mayo Clin. Proc. 78 (2003) 901–907, https://doi.org/10.4065/78.7.901.
[39] JCS Joint Working Group, Guidelines for diagnosis and treatment of myocarditis (JCS 2009): Digest version, Circ. J. 75 (2011) 734–743, https://doi.org/10.1253/circj.cj-88-0008, 2011.
[40] L.T. Cooper, K.J. Zehr, Biventricular assist device placement and immunosuppression as therapy for necrotizing eosinophilic myocarditis. Nature Clinical Practice, Cardiovasc. Med. 2 (2005) 544–548, https://doi.org/10.1038/ncpcardio0322.
[41] E. Ammirati, M. Stucchi, M. Brambatti, F. Spanò, E. Bonacina, F. Recalcati, G. Cerea, A. Vanzulli, M. Frigerio, F. Oliva, Eosinophilic myocarditis: a paraneoplastic event, Lancet 385 (2015) 2546, https://doi.org/10.1016/S0140-6736(15)60903-5.
[42] M. Take, M. Sekiguchi, M. Hiroe, K. Hirosawa, H. Mizoguchi, M. Kijima, T. Shirai, T. Ishide, S. Okubo, Clinical spectrum and endomyocardial biopsy findings in eosinophilic heart disease, Heart Ves. Suppl. 1 (1985) 243–249, https://doi.org/10.1007/BF02072403.
[43] S. Hayashi, M. Isobe, Y. Okubo, J. Suzuki, Y. Yazaki, M. Sekiguchi, Improvement of eosinophilic heart disease after steroid therapy: successful demonstration by endomyocardial biopsied specimens, Heart Ves. 14 (1999) 104–108, https://doi.org/10.1007/BF02481750.
[44] A. Aggarwal, P. Bergin, P. Jessup, D. Kaye, Hypersensitivity myocarditis presenting as cardiogenic shock, J. Heart Lung Transplant. 20 (11) (2001) 1241–1244, https://doi.org/10.1016/s1053-2498(01)00313-8.
[45] Y. Yamaguchi, Y. Hayashi, Y. Sugama, Y. Miura, T. Kasahara, S. Kitamura, M. Torisu, S. Mita, A. Tominaga, K. Takatsu, Highly purified murine interleukin 5 (IL-5) stimulates eosinophil function and prolongs in vitro survival. IL-5 as an eosinophil chemotactic factor, J. Exp. Med. 167 (1988) 1737–1742, https://doi.org/10.1084/jem.167.5.1737.
[46] T. Song, D.M. Jones, Y. Homsi, Therapeutic effect of anti-IL-5 on eosinophilic myocarditis with large pericardial effusion, BMJ Case Rep. (2017), https://doi.org/10.1136/bcr-2016-218992.
[47] D. Broide, J. Schwarze, H. Tighe, T. Gifford, M.D. Nguyen, S. Malek, J. Van Uden, E. Martin-Orozco, E.W. Gelfand, E. Raz, Immunostimulatory DNA sequences inhibit IL-5, eosinophilic inflammation, and airway hyperresponsiveness in mice, J. Immunol. 161 (1998) 7054–7062.
[48] E.M. Chau, W.H. Chow, C.S. Chiu, E. Wang, Treatment and outcome of biopsy-proven fulminant myocarditis in adults, Int. J. Cardiol. 110 (2006) 405–406, https://doi.org/10.1016/j.ijcard.2005.07.082.
[49] D.M. McNamara, R. Holubkov, R.C. Starling, G.W. Dec, E. Loh, G. Torre-Amione, A. Gass, K. Janosko, T. Tokarczyk, P. Kessler, D.L. Mann, A.M. Feldman, Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy, Circulation 103 (2001) 2254–2259, https://doi.org/10.1161/01.cir.103.18.2254.
[50] S. Kawano, J. Kato, N. Kawano, Y. Yoshimura, H. Masuyama, T. Fukunaga, Y. Sato, H. Maruyama, K. Mihara, A. Ueda, K. Toyoda, T. Imamura, K. Kitamura, Clinical features and outcomes of eosinophilic myocarditis patients treated with prednisolone at a single institution over a 27-year period, Internal Medicine (Tokyo, Japan) 50 (2011) 975–981, https://doi.org/10.2169/internalmedicine.50.4079.